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THE HEMORRHAGIC DISEASE OF THE NEW BORN

BY

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THE UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

INTRODUCTION:

1

The Hemorrhagic Disease of the New Born is a distinct disease entity, characterized by a marked tendency for new born infants to bleed during the first week of life. Both clotting and bleeding time are definitely prolonged before there are any hemorrhagic manifestations. The essential symptom is the spontaneous escape of blood from small blood vessels, in any organ or structure of the body, evident or concealed, unassociated with delivery, syphilis, sepsis or any other process.

The nomenclature is complex and confusing. Terms found in the literature are Melena, Hemorrhagic Diathesis, Omphalorrhagia Neonatorum, Hemophilia Neonatorum. Names applied to the site of bleeding have led to terms as Purpura of New Born (hemorrhage in skin), Melena (intestinal tract), Omphalorrhagia (umbilical cord), Hepatic, Adrenal and Cerebral Hemorrhages.

Much of the confusion in the literature, especially regarding etiology, arises from the failure of many observers to clearly differentiate between the various hemorrhagic conditions in the new born.

This discussion deals with the type of spontaneous hemorrhage in new born infants, not inherited, nor secondary to any other disease, but due to a decreased blood clotting function.

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HISTORY:

2

Although the manifestations of the Hemorrhagic Disease of the New Born are among the oldest known to man, our knowledge of it is comparatively recent.

Probably it's first mention in the literature was by Mauriceau in 1682.

In Cheyne's "Essays on the Diseases of Children" published in Edinburgh in 1801, there was a description of a well marked case with a colored plate illustrating postmortem changes.

In 1850, Henry I. Bowditch of Boston reported twelve cases of hemorrhage from the umbilicus with a description of signs and symptoms. Two years later Francis Minot of Boston described the condition with an analysis of forty-six cases, 84 percent of which were fatal.

In 1891, Townsend reported a series of thirty-two cases with an accurate description of the disease, to which he gave the name "The Hemorrhagic Disease of the New Born", by which it is now known. In 1894, he (41) reported fifty cases of bleeding in new born that were self limited and definate in character. He classified them as to site of hemorrhage and observed that in all but three the bleeding showed itself during the first seven days of life, the majority beginning on the second or third day. He suggested an infectious origin.

In 1906, Lequex in his "Paris Thesis" (quoted by 27) illustrated the confusion and lack of knowledge of this condi-

tion, by presenting four stages of historical interest and study.

1. Up to 1825 - Period of Confusion.

2. 1825 to 1835 - Period of Clinical Observation.

Widely varying causes were cited. Too late tying of the umbilical cord had it's supporters, while too early ligature was as warmly advocated by others.

3. 1835 to 1875 - Period of Pathologico - Anatomic Studies. A variety of lesions such as embolism, ulceration, patent ductus arteriosus were found associated with hemorrhage and considered as the cause.

4. 1875 to 1906 - Period of Laboratory Study. This being the period of early development of bacteriology, it is not strange that nearly every pathogenic bacteria was at one time or other considered as the agent producing the disease.

5. The Present Period - beginning with 1908. This has been concerned largely with studies of the physiology of blood coagulation.

INCIDENCE:

Great variation of opinion exists regarding the frequency with which this condition occurs.

In 1894, Townsend (41) in reporting fifty cases considered the incidence about 0.57 percent in all births, with the distribution between sexes about equal.

Warwick (43) in a study of eighty-one infants at Miller Hospital, St. Paul, Minnesota, found that 3.7 percent developed symptoms of Hemorrhagic Disease of the New Born.

Schloss and Commiskey (31) considered that the condition varied in frequency from 1 in 1800 to 1 in 116 births.

At the Jefferson Hospital in Philadelphia (6) one case occurred in every 1200 births and at the Philadelphia Lying-In Hospital (6) one in every 1897 births.

At the New Born Clinic at the University of Minnesota (27) one case occurred in every 100 births. Most observers (16) consider the latter more nearly the actual incidence.

Cerebral hemorrhage is the cause of death in more than fifty percent of infants dying intrapartum or within a few days after birth. Hemorrhagic Disease of the New Born is the causative factor in from twenty-five percent (26) to forty-four percent (44) of these cases.

Much of the above discrepancy arises, due to the fact that early observers took note only of the cases of external bleeding and overlooked the internal hemorrhages.

ETIOLOGY AND PATHOLOGY:

During the earlier periods of investigation, Hemorrhagic Disease of the New Born was ascribed to widely varying causes. Among these were asphyxia from prolonged labor, general plethora, congestion of the mesenteric arteries, respiratory embarrassment, vascular thrombosis, rupture of blood vessels, irritation due to swallowed amniotic fluid and too early ligation of the umbilical cord. The occurrence of melena, was explained on the basis of inflammation of the gastro-intestinal tract, or originating from ulcers or erosions of the mucus membranes.

Many of the early writers considered haemophilia as a frequent cause of spontaneous hemorrhage in the new born. Grandidier reported that in 6.0 percent of cases he found haemophilia, either from a distinct history, or they recovered and remained bleeders in later life. It has since been found however, that haemophilia is rarely manifested in the new born, and while the coagulation time is prolonged, the bleeding time is normal.

About the time bacteriological studies were so successful in revealing the cause of many morbid conditions, search was made for a specific microorganism as the etiological factor in this condition. Townsend (41) in 1894 in reporting a series of 50 cases, noted that 12 infants in this series had a temperature of 101 - 103, the temperature dropping to normal or below on cessation of the hemorrhage. He concluded that this suggested the condition as being of an infectious character.

Nicholson (49) reported that in 1500 births at the Sloan Maternity Hospital during a period free from puerperal infection, there were no cases of hemorrhage, but in a subsequent 225 deliveries during the prevalence of puerperal infection, there were eight cases of hemorrhage.

Klebs (quoted by 31) in 1875 described an organism and called it "Monas Hemorrhagicum" which he found in the tissues of an infant dying as the result of hemorrhage.

Following this various other organisms were isolated and described. The results were very inconstant, the pus cocci, *B. coli*, *B. typhosus*, *B. enteritidis*, *B. lactis aerogenes*, Klebs Loeffler bacillus, Freidlander's bacillus were among the organisms recovered on autopsy. An objection (31) to many of the bacteriological examinations may be made in that the evidence in most cases rested on postmortem findings, 12-24 hours after death and may thus have represented postmortem invasions. No specific organism that was constantly present was demonstrated. Thus these findings merely indicate that hemorrhage may occur during the course of bacterial infection.

Syphilis was considered by other observers as an etiological factor. An objection (31) raised was that observers were unable to demonstrate vascular changes in syphilitic infants.

Cerebral injury was another factor considered, but this seemed improbable (31) since there were cases of gastrointestinal hemorrhage observed in which there was no evidence of brain injury. Intracranial hemorrhage was later considered a symptom and not a cause.

Weber (quoted by 2) in Germany, about 1850, observed a great delay in the coagulation of the blood and referred to the futility of local measures in controlling the hemorrhage. Other observers (31) noticed that in many cases the blood remained fluid for many hours after death.

Lucas (48) and other writers then suggested that the continued hemorrhage was dependent on delayed or incomplete coagulation of the blood.

Schloss and Commisky (31) found in two cases that there was no coagulation in one half and one and one-half hours. The patient however recovered, and then the coagulation time was found to be four minutes in both cases. They reported 5 additional cases, which undoubtedly were not true cases of Hemorrhagic Disease of the New Born, in which there was no marked change in the coagulation time during the hemorrhage, and after recovery. They concluded that absent or delayed coagulation time was not constant. They considered that when the coagulation time was normal yet hemorrhage occurred, that it was because retraction of the clot was defective or absent.

In 1908 Lambert (20) reported a case of hemorrhage in an infant eight hours after birth. The bleeding began from the umbilical cord, three hours later there was epistaxis and a temperature elevation to 102.2. Thirty minims of olei ricini and two grains of calcium lactate was given every two hours, but without effect. The infant became exsanguinated. Four days later as a last resort, a direct transfusion from the father, by end to end anastomosis was given. The symptoms were relieved almost immediately. Lambert decided that such a sudden change in condition, could

not be due to a structural regeneration in the capillary vessels, nor to a sudden overcoming of infection. The only possible explanation of so rapid a change, must be found in a chemical condition of the blood.

Schwartz and Ottenberg (33) in 1910, reported two cases of hemorrhage in new born in which the bleeding was uncontrollable, and the coagulation slow or absent. They concluded that impaired coagulation was the immediate cause of this hemorrhage, probably due to destruction of, or interference with the production of thrombokinese.

Out of all the previous confusion regarding etiology, Schloss and Commiskey (31) have brought out a simple understandable classification regarding hemorrhage in the new born.

1. Traumatic - obstetrical or surgical procedures.
2. Accidental - insecure tying of cord etc.
3. Spontaneous (a) Symptomatic - sepsis, congenital syphilis or haemophilia.

(b) Idiopathic.

The idiopathic is the true Hemorrhagic Disease of the New Born as first suggested by Townsend (41). This is characterized by spontaneous bleeding on the first, second or third day after birth, unassociated on the first appearance of the bleeding by any other symptoms.

Townsend (41) in an analysis of 50 cases, found that in all but 3 cases, the bleeding showed itself during the first seven days of life, the majority of cases beginning on the second or third days. Beveridge (4) in 18 cases of hemorrhage in which no source of sepsis was found, nor any lesion suggesting syphilis, everything being normal; found that the bleeding in all cases began on or before the fifth day, the majority beginning on the second day.

Rodda (25, 26) determined the coagulation time on 126 normal new born infants within the first twenty-four hours and found this to average seven minutes, with an arithmetical deviation of one and one-half minutes, giving an approximate range of five and one-half to eight and one-half minutes. More than ten minutes means delayed coagulation. He noted that the coagulation time varied on different days, there being a tendency to prolongation over the second, third and fourth days, with a maximum on the fifth day, and a return to the time of the first twenty-four hours before the tenth day.

A study was also made of the bleeding time, and in 126 cases the average time was three and one-half minutes. A range of two to five minutes may be considered normal.

Beveridge (4) made similar observations on normal new born infants at the Glasgow Maternity Hospital. The average coagulation time in seconds on the first day was

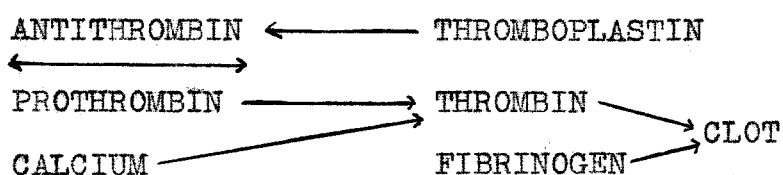
118.2, second day 139.6, third day 137.0, fourth day 134.5, fifth day 123.5, sixth day 115.9, seventh day 119.4, eighth day 108.3., ninth day 104.7, tenth day 103.4. The average bleeding time was two and one-half minutes. Other investigators (44) (48) have made similar observations.

The greatest incidence of Hemorrhagic Disease of the New Born is on the second to fifth days, thus corresponding with the period in which there is normally a prolongation of the coagulation time. It has been suggested that the pathogenesis, may in part be dependent on a delay in reaching the normal level.

Rodda (25) studied a series of cases presenting a coagulation time above the normal range. All these cases presented an exaggeration of the normal curve of the coagulation time. In two cases a prolonged bleeding time accompanied the delayed coagulation time. Cases showing prolonged coagulation time and normal bleeding time, showed no hemorrhage. It would appear therefore that the hemorrhagic factor is a complex of delayed coagulation time and prolonged bleeding time. The variations from the normal range of coagulation and bleeding times, are due to some deficiency of coagulation properties, or excess of anti-clotting substances, which may gradually be overcome. This may be hastened by the subcutaneous administration of blood. In all cases a return to normal findings occurred on the 10th day.

Sherman and Lohnes (34) studied the blood daily for five days in 100 cases. Taking Rodda's figures of 9 minutes for the upper limit for clotting, and 5 minutes for the upper limit of bleeding time; they found 28 cases in which the bleeding time, and 12 cases in which the clotting time was prolonged. One case had a clotting time of 10 minutes, four of 11 minutes, one of 12, one of 13, two of 14, two of 15 and one of 16 minutes. Nine cases showed a bleeding time of 6 minutes, five of 7, five of 8, one of 9, one of 10, two of 11, one of 13, one of 23, one of 25, and two of one hour. All cases returned to normal before the 10th day. Their cases showing bleeding, were characterized by a prolonged bleeding rather than clotting time. They concluded that there might be two conditions present. One in which there is a failure of the clotting process, and the other in which the fault lies in the vessel itself. Although the blood clots, there is something lacking in the clot, which causes it to fail to adhere to the vessel wall, and by its contraction to seal the vessel.

Before considering the deficiency in the mechanism of coagulation in Hemorrhagic Disease of the New Born, it may be well to give a brief account of Howells (13) (14) theory of the normal coagulation of blood. A graphic presentation would be as follows:



The circulating blood contains normally all the necessary fibrin factors, namely, fibrinogen, prothrombin and calcium. These substances are prevented from reacting, and the normal fluidity of the blood is maintained by the fact that antithrombin is also present, and this substance prevents the calcium from activating the prothrombin to thrombin. In shed blood, the restraining effect of the antithrombin is neutralized by the action of a substance - thromboplastin, furnished by the tissue elements. In mammalia the thromboplastin is derived from the elements of the blood itself - blood platelets. In the lower vertebrae, the supply of thromboplastin in normal clotting, comes from the external tissues.

When clotting takes place, the thromboplastin which has been set free by cell injury, neutralizes the antithrombin. This frees the prothrombin, which at once combines with calcium to form thrombin. The free thrombin coagulates the fibrinogen, forming fibrin and giving the normal clot. It is evident, that this balance of antithrombin and prothrombin must be extremely delicate, and capable of rapid adjustment.

Kugelmass (17) has contributed the most recent explanation of the clotting mechanism. He believes that the blood plasma so long as its constituents are not dissociated by extraneous forces, is a single complex in equilibrium, rather than a mixture of substances. Blood when shed, has

Prothrombin is electro negative in the blood, and acts as a nucleus of electrical condensation of the clotting components in the formation of a gel. It's concentration is directly proportional to the clotting activity of the blood.

An adequate platelet count with rapid disintegration, liberating phosphatides, is also necessary.

Fibrinogen constitutes the potential clot structure, dispersed in the plasma in the most readily precipitable form. It's transformation into fibrin completes the clotting reaction.

Whipple and Hurwitz (50) in 1911 made the first attempt by means of experimental work to determine the deficiency in the mechanism of coagulation in Hemorrhagic conditions of the New Born. In their work with the infants blood they found that the addition of calcium chloride did not produce coagulation. Hence there was no deficiency of calcium.

The addition of normal, defibrinated human blood, caused the infants blood to coagulate completely in three to four minutes; showing there was no deficiency of fibrinogen, and also that an antithrombin was not the cause of the delayed coagulation. Defibrinated blood contains both thrombin and thrombokinase.

Defibrinated human blood, which had been heated to 60 - 63 degrees centigrade for 35 minutes to destroy the preformed thrombin, caused the infants blood to clot in six to seven minutes. Coagulation however, was incomplete,

and the resulting clot soft and gelatinous.

They concluded that the deficiency was due to a lack of thrombokinase, but that their results were not conclusive, since Howell (13) had shown in 1910, that he had obtained a pure thrombin under conditions in which even greater heat had been used. Hence the preformed thrombin may not have been destroyed.

In 1912 Whipple (46) reported a case of Hemorrhagic Disease of the New Born. The infant was normal until the second day, when bloody stools were passed with symptoms of internal hemorrhage. Bleeding from the nose and fore-skin occurred on the fourth day, with death the same day. There was no evidence of septicemia or syphilis, which was substantiated by histological studies. Autopsy, two hours after death, showed no clots in the vascular system. There was evidence of hemorrhage in the intestine, lungs and spleen. Fibrinogen and calcium were found present, and various tests gave no evidence of the presence of antithrombin. Thrombin was tested and found absent. It was concluded that the absence of blood coagulation was due to an absence of thrombin or prothrombin.

Examination of the lung showed the presence of old fibrin but no fresh fibrin. Thus, a few days previous to death the tissues were able to coagulate the fibrinogen and form fibrin - a process impossible during the last two

days of life. This shows that prothrombin had been present in the blood at birth, becoming absent during the first few days of life. Study of the case offered no anatomical evidence to explain the disappearance of prothrombin.

In 1913, Whipple (47) reported a detailed blood examination, of a child dead of Hemorrhagic Disease of the New Born. The infant's plasma was readily clotted by fresh serum or pure thrombin. Fibrinogen and calcium were present in normal amounts, with an abundance of thromboplastin. The infant's plasma did not delay the coagulation of normal plasma, thus showing an absence of any antithrombin excess. The results were conclusive, in proving that the only blood abnormality was the absence of prothrombin. The beneficial effect following injection of whole blood, is a result of supplying this missing factor.

Kugelmass, (16)(17) believing that the quantitative determination of the dissociated compounds involved in blood coagulation, offers a basis for evaluating the clotting function of the blood; determined the relative composition of the blood clotting constituents, in an infant with Hemorrhagic Disease of the New Born, as compared with a normal infant. The prothrombin was 0.1 compared to a normal of 1.0, fibrinogen 0.6 with a normal of 0.5, antithrombin was 1.0 in both, platelets 280,000 with a normal of 250,000,

and percentage of platelet disintegration 40 with a normal of 50. He devised a formula to determine the clotting index:

(PROTHROMBIN) X (FIBRINOGEN)

$$\text{INDEX} = \frac{\text{PROTHROMBIN} \times \text{FIBRINOGEN}}{\text{ANTITHROMBIN}}$$

Introducing normal values for these substances, the normal index is found to be 0.5. Values over 1.0 indicate a marked tendency to clot, and values below 0.2 indicate a marked tendency to bleed. The index in the infant with Hemorrhagic Disease of the New Born was 0.06. This index reveals the true blood status, as a fundamental basis for the characterization of this hemorrhagic disturbance.

Thrombin (46) injected into normal animals does not cause intravascular clotting, but an antithrombin production, which neutralizes the dangerous excess of thrombin at once. When blood (thrombin) is injected into infants in this condition, this phenomena does not take place, since we are not dealing with a normal blood. In normal blood, the prothrombin is present, but anchored or fixed by the normal antithrombin present in sufficient amount for this purpose. In Hemorrhagic Disease of the New Born, the prothrombin is lacking, and this normal balance is absent - the antithrombin is not bound or satisfied. When blood (thrombin) is introduced, a necessary part of the thrombin will enter into combination with the unsatisfied or unbound antithrombin normally present, and the excess of thrombin will be neutralized in the normal manner. Now the equilibrium of

the blood, the normal balance of antithrombin and thrombin or prothrombin, is established; so the circulating blood is in a position to react normally to any injury causing a production of thromboplastin.

It has been definitely established that there is a deficiency of prothrombin, and a disturbance of the antithrombin - prothrombin balance. But this deficiency of prothrombin has not been explained. It has been shown that it is present at birth, and then suddenly disappears from the infant's blood stream, and that the clinical manifestations of Hemorrhagic Disease of the New Born then ensue. In an approach to this problem, it may be well to first consider the origin of these substances.

According to Howell, (13) (14) both antithrombin and fibronogen are formed in the liver.

Thromboplastin seems closely related, if not identical with cephalin. It is derived from the platelets but also from the tissue cells. Prothrombin also seems to be derived from the platelets, which when activated forms thrombin. The platelets are lipoidal protoplasmic separations from megakaryocytes in the bone marrow. Kugelmass (1) in a more recent contribution, states that it has been established, that prothrombin is a globulin synthesized in the liver.

Warwick (44) found that the platelet count was decreased, and showed a curve corresponding to the curve of bleeding and coagulation time. Other observers, (51,21)

(48, 15, 34) have since shown that the platelets are not reduced in number, and that there is no correlation between platelet count and coagulation or bleeding time. There is, however, evidence (21,48) to show that there are qualitative changes in the blood platelets. Lucas (48) believes this is the basis of the normal prolongation of clotting in the first five days - producing a lack of prothrombin. An exaggeration of this being the basis of hemorrhage.

Sooy and Moise (39) used the quartz lamp in Hemorrhagic Disease of the New Born with benefit, the platelet count increasing tremendously.

Sanford (29) found that short exposures to ultra violet light lowered the bleeding time of the blood in new born infants, did not affect the coagulation time, and increased the platelet count, but only temporarily. This coincides with the observations of McCallum (22) in Toronto, Canada, who noticed that the greatest incidence of the disease occurred, when the ultra violet rays of the sun were scarcest. He concluded that since ultra violet light tends to conserve at least one vitamine, that it is quite possible that the lack of prothrombin is brought about by a lack of vitamine B. in the infant's blood. It has been shown (23) experimentally in rats, that avitaminosis is a cause of hemorrhage in the new born. In the case of an

infant developing Hemorrhagic Disease of the New Born, the mother's diet was found markedly deficient in water soluble vitamine B.

Kugelmass (19, 18) further shows the relationship of diet to Hemorrhagic Disease of the New Born. A mother who had lost her four previous children from this disease, entered upon her fifth pregnancy. A deficiency of prothrombin was demonstrated in her blood during the second month. She was placed on a high protein diet, and at full term was delivered of a normal infant, that developed no symptoms of hemorrhage.

That it is not entirely a matter of such dietary deficiencies, was shown by Sanford (30) who reported a twin birth without anesthesia, in which hemorrhage developed in one, and not in the other. He further showed, that nitrous oxide used during labor caused a prolongation of the average bleeding time at birth of one minute, and of the coagulation time of two minutes. Ethylene prolonged the average bleeding time two minutes, and the coagulation time three minutes. In both instances, bleeding and coagulation time were normal by the ninth day. The manner in which the anesthetics produce their effect, is undetermined. It maybe because of a common property, such as partial asphyxia, which Graham (11) concluded was the basis of the hemorrhage in new born infants following the use of chloroform anesthesia. Both suggest that some pathologic

change in the liver may be responsible.

It has been previously shown (1, 13, 14) that anti-thrombin, fibrinogen and prothrombin are all synthesized in the liver. Sherman and Lohnes (34) have suggested that the deficiency of prothrombin may result from the effect on the function of the liver, produced by the circulatory change immediately following birth. That it does not occur more frequently, being due to the fact that only from 15 to 20 percent of the normal quantity of liver tissue is necessary to meet the ordinary body needs. The objection to this could be made, that under the same influences, the liver might produce substances that would both accelerate and retard coagulation.

It seems improbable that any of these factors play a part in the causation of Hemorrhagic Disease of the New Born. The clear cut features of this disease makes it seem likely that a single cause or set of causes, the same in each instance, is operative. However, the underlying basis of the blood change in Hemorrhagic Disease of the New Born, still remains undetermined.

SYMPTOMS AND DIAGNOSIS:

The average new born infant is in a transitional period between release from the obstetrician and supervision by the pediatrician, with consequent diffusal of medical responsibility, and unnecessary delay in problems pertaining to hemorrhagic disease. Careful daily observations of the mode of adaptation of the new born infant to the new order of things, is indispensable for recognizing early manifesta-

tions of potential disease, constitutional, acquired or secondary to the birth process.

Bleeding (16) from any source in the new born, is either the result of vascular injury, or of actual disturbance in the clotting mechanism. The most frequent hemorrhagic manifestations in the new born during the first few days of life, are due to the physiologic hyperemia, which may be so marked that rupture of the small blood vessels occurs, with extravasation of blood into the tissues. When symptoms indicative of infection are associated with the bleeding, it may also be due to sepsis or syphilis.

However, when there is continuous oozing of blood from any part of the body, on the first to third days after birth, unassociated on the first appearance of the bleeding by any other symptoms, it is usually constitutional in origin, and referable to Hemorrhagic Disease of the New Born. Daily clotting and bleeding time determinations of all new born infants, should be made whenever there appears the slightest bleeding from any source, or if there are symptoms indicative of concealed hemorrhage.

Many authorities (43,40, 25, 8, 21), consider that clotting and bleeding time determinations, should be made routinely on every new born infant on the first,

third and fifth days, so that a diagnosis of potential hemorrhagic disease may be made before bleeding or symptoms occur, and a prophylactic injection of blood administered. Since a diagnosis can be made much earlier from blood studies, than from the symptoms.

Rodda, (25) devised a simple clinical method for determining the coagulation time in infants. It consists in collecting one drop of blood, in a clean watch glass containing a No. 16 lead shot. The end point of coagulation occurs, when the shot is caught up on the fibrin and no longer rolls. This simple practical method detects only gross variations from the normal range. This, however, is sufficiently accurate for diagnosis.

Duke, (7) likewise devised a simple method for testing the bleeding time, which is quite independent of the coagulation time. The ear is punctured with a sharp needle, and the blood wiped up every minute by blotting paper. The end point occurs when the bleeding ceases.

By these methods, determinations (25,26, 4) on normal new born infants have shown, that the normal coagulation time varied from five and one-half to eight and one-half minutes, during the first twenty-four hours, with a tendency for prolongation over the second, third and fourth days, reaching a maximum on the fifth day, and

a return to the time of the first twenty-four hours before the tenth day. The bleeding time showed a normal range of two to five minutes. Thus more than ten minutes means delayed coagulation, and over five minutes means prolonged bleeding time.

When there is prolonged coagulation time but normal bleeding time, no hemorrhage occurs. The hemorrhagic factor is a complex of delayed coagulation and prolonged bleeding time.

The greatest incidence of Hemorrhagic Disease of the New Born is on the second to fifth days, thus corresponding with the period in which there is normally a prolongation of the coagulation time.

The tests devised by Rodda and Duke are simple, require no elaborate equipment, and can be done by any one. If these determinations were made routinely in every case, a diagnosis could be made early, and if the coagulation time exceeds ten minutes, or the bleeding time five minutes, proper treatment could be instituted and the disastrous after effects and sequelae avoided.

Thus (16) we see that this is a distinct disease entity, characterized by a marked tendency for new born infants to bleed during the first week of life. It is further characterized by a definite prolongation of both clotting and bleeding time, before there are any hemorrhagic manifestations. It is due to a decreased

clotting function, not inherited, nor secondary to any other disease. These simple determinations are diagnostic either of potential, or actual Hemorrhagic Disease of the New Born.

Kugelmass and Tritsch (19) (1) have carried on investigations along the line of prenatal prevention of potential Hemorrhagic Disease of the New Born. It is known that in this condition, the prothrombin of the infants blood is below normal in quantity. They believe that since the blood of the foetus is in equilibrium with the maternal blood, any deviation in the concentration of the clotting components, would be manifest in the maternal blood, studied early in the course of pregnancy. The evaluation of the blood clotting function of maternal blood, would thus offer a basis of prediction of potential Hemorrhagic Disease of the New Born developing in utero. Such an early diagnosis would be more favorable for prenatal preventative therapy.

They cite a case where blood examination during the second month of pregnancy, showed a low prothrombin and fibrinogen content. As a result of this early diagnosis, the mother being placed on the proper dietary regimen, she was delivered of a normal infant at full term. Her four previous babies had all died of the disease.

This, however, offers little in the way of diagnosis, since this procedure is too complicated for routine use.

The essential symptom is spontaneous bleeding, coming from almost any mucus surface, or into any organ of the body. The onset is usually on the second or third day and is unassociated with delivery, syphilis, sepsis or any other process.

The hemorrhage may be subcutaneous, hence the term Purpura of New Born; or from the umbilical cord. The hemorrhagic tendency may be latent, until an abrasion of the skin, opening of a hematoma, forcible removal of a clot or circumcision, give occasion for protracted bleeding.

In concealed bleeding (4) , the hemorrhage may occur into the abdominal viscera and very confusing clinical signs and symptoms ensue. When the hemorrhage is into the lungs, the infant may become dyspneic or cyanotic with usually a temperature elevation, vomiting and refusing to nurse. The infant becomes restless, there is a marked pallor and finally prostration - all the signs of a severe secondary anemia.

When the bleeding is in the gastro-intestinal tract, the stools may show clear blood or be black and tarry. There may be a dark brown vomitus if the bleeding comes from the nose, mouth or stomach.

The hemorrhage may also be cerebral (40) in location and develop insiduously. The infant becomes drowsy or irritable, has difficulty in swallowing and later refuses to nurse. There may be muscular twitching with retraction of the head, convulsions or paralysis. Examination of the

fontanelles may disclose a distention and tenseness, at times of a board-like degree, or actual bulging with loss of pulsation. The sutures may be separated and the veins of the eyelids and forehead prominent and dilated. With a moderate degree of cerebral compression the pulse is slow, but when medullary paralysis is imminent it becomes rapid. Frequently there is inequality of the pupils and ocular palsies. There may be (27) marked disturbances of respiratory and cardiac rhythm with vasomotor symptoms.

Cerebral hemorrhage (44, 26) is the cause of death in more than 50 percent of infants dying intrapartum, or within a few days after birth; and more than half are due to Hemorrhagic Disease of the New Born.

Townsend (41) and Beveridge (4) classified a series of 74 cases of Hemorrhagic Disease of New Born, as to sources of hemorrhage. They found that hemorrhage from the intestines occurred in 37 cases, stomach in 29, mouth in 19, nose in 16, umbilicus in 25, ecchymosis of skin in 32, scratch of skin in 1, cephalhematoma in 3, meningeal in 5, abdominal cavity in 4, pleural cavity in 2, pulmonary in 6, thymus in 2, pericardium in 2, and from the kidneys in one case. In 5 cases hemorrhage occurred simultaneously from the gastrointestinal tract, nose and umbilicus with ecchymosis in the skin. In 20 cases the hemorrhage was from the gastrointestinal tract alone, in 3 cases from the umbilicus alone

and in 6 cases the only signs of bleeding, were ecchymosis in the skin.

The essential feature is bleeding which may be from almost any part of the body, the exact symptoms depending upon the site and degree of hemorrhage. In all cases where any doubt or confusion exists, coagulation and bleeding time determinations are definitely diagnostic.

TREATMENT:

Hemorrhagic Disease of the New Born was originally treated locally by various means; as by the use of ergot, hydrastis, adrenalin, ice water, or by the administration of calcium or gelatin by mouth. The results were universally disappointing, with a mortality according to various observers (41, 21, 15, 2), ranging from 50 to 85 percent.

The first notable advance in treatment was in 1908 when Lambert (20), reported a transfusion in a severe case of Hemorrhagica Neonatorum. An anastomosis was made between the right popliteal vein of the infant, and the left radial artery of the father, and enough blood allowed to flow into the infant to change the skin from a pale, transparent whiteness to a brilliant red color. There was almost immediate cessation of the hemorrhage, and the infant made an uneventful recovery.

Welch in 1911 (quoted by 21) first showed the value

of subcutaneous injections of human blood serum. In a series of nine cases only one died.

During the same year Schloss and Commiskey (31, 32) introduced the subcutaneous use of whole human blood, injecting 10 to 30 cc. every four to eight hours, with remarkable results. This method of treatment was universally adopted and lowered the mortality (21) to 10 or 15 percent.

Determinations (28) of the blood clotting time of every infant, should be made within the first few hours of life, and again on the third or fourth days. Any clotting time over ten minutes, with or without symptoms, calls for an immediate injection of whole human blood. Then the clotting time should be determined every six hours, until it goes to ten minutes and remains there. This should be a routine procedure in every infant. At least 20 cc. fresh human blood should be injected subcutaneously, since Greb (12) in determining the value of subcutaneous injections of whole blood, in a series of 125 new born infants, found that 10 cc. produced but little effect on the bleeding or coagulation time.

If hemorrhage has already occurred, the treatment depends largely on the severity of the bleeding. If much blood has been lost, the general treatment (24) is like that of any other case of hemorrhage or shock. The infant should be kept quiet, handled and moved about as

little as possible. Heat should be applied to the body. If the symptoms are marked or the infant is weak, milk should be expressed from the mother's breast and fed by a medicine dropper or by gavage.

If the hemorrhage is mild, many observers (15, 2) consider the subcutaneous injection of 15 to 30 cc. of whole human blood every four to six hours as adequate. When the infant's condition is serious (21) a transfusion should be done. About 15 percent of the body weight, is considered a safe amount of blood to transfuse at one time, if given slowly. This amounts to 10 or 15 cc. per pound of body weight. Battley (2) considers 15 cc. per kilogram of body weight as the proper amount for transfusion.

Kugelmass, (16) believes that a transfusion should be given even in mild cases, since they may rapidly become severe, and the risk of a destructive intracranial hemorrhage should not be encouraged. He considers a transfusion of 50 to 100 cc. of citrated blood satisfactory. If the hemorrhagic condition is urgent, 30 cc. of blood may also be injected subcutaneously or intramuscularly, into each buttock, twice a day until the bleeding ceases. The subcutaneous or intramuscular injection requires no preliminary typing, but when the blood is administered

intravenously. agglutination tests should be made, because the serum of some new born infants contains agglutinins for adult corpuscles. The bleeding usually stops within twelve hours and a second transfusion is rarely necessary. This, however, is true only when the condition has been recognized early.

Galbraith and Lewis (9), on the other hand, state that Biasi typed the blood of 100 mothers and their children, and in no case, found the maternal corpuscles agglutinated by the serum of the child.

Coppolino (6) considers the intraperitoneal injection of 20 to 30 cc. of blood, an excellent method, since it requires no typing, and also is devoid of the difficulties encountered so frequently, in attempting to enter the vein of a new born infant.

The best site for transfusion depends largely on the blood vessel that the individual operator finds most accessible. The external jugular veins, (9) internal saphenous veins, median basilic veins are suggested. Frequently great difficulty is encountered in entering these veins and the superior longitudinal sinus (3) is found more accessible.

Sidburg (36) considers the umbilical veins patent and accessible for transfusion up to, and including the fourth day of life. Since Hemorrhagic Disease of the New Born

usually manifests itself prior to the fifth day, this is a route that may be utilized in this condition. Since no difficult technique is required, it is particularly appropriate for the inexperienced operator, who might experience difficulty in entering the superior longitudinal sinus. There is always the possibility that transfusion into the sinus, in cases of intracranial hemorrhage, might increase intracranial pressure.

When there are symptoms of intracranial hemorrhage, the pressure may have to be reduced by puncture, but this should not be done unless urgent, until the injected blood has had time to increase the clotting power of the patients blood. Otherwise a fresh hemorrhage may result.

In case of severe intracranial pressure, Strachauero (40) advises a decompression operation, and believes this usually to be sufficient, without disturbing the clot. The delicate brain tissue of the infant withstands the effect of pressure poorly. The architecture of the infant's skull is planned to relieve a certain degree of increased intracranial pressure, being partially distensible by means of the broad sutures and the fontanelles. The fontanelles may be termed nature's prophylactic decompression. This provision, however, suffices for only the mildest degrees of increased pressure beyond which operative decompression must be performed, to prevent the

degeneration of the brain or the impending medullary paralysis, in the more severe hemorrhages. This can all be avoided by routine coagulation and bleeding tests, and the prophylactic injection of blood when both are found prolonged.

While it is unlikely that the actual treatment of Hemorrhagic Disease of the New Born will be changed by newer knowledge, prophylaxis will undoubtedly become more important. Some further work along this line is of interest.

Sanford (29) in a study of 50 new born infants found that short exposure to ultra violet light lowered the bleeding time, but did not affect the coagulation time. The platelets were increased only temporarily. He concluded that short exposure to ultra violet light would serve as a therapeutic measure in infants with increased bleeding time, but that their coagulation time would have to be decreased by other means.

McCallum (22) made similar observations. In the hospital for sick children at Toronto, there is a definite increase of cases about October 1st, a maximum number in January, falling rapidly by April 1st and remaining low throughout the summer. This corresponds to the variation in the ultra violet light of the sun's rays. He advises the use of ultra violet light as a prophylactic measure.

Moore and Brodie (23) consider avitaminosis as a cause

of hemorrhage in the new born, and advise the addition of foods rich in water soluble vitamins "B" to the mother's prenatal diet. McCallum (22) holds a similar view.

Kugelmass and Tritsch (19, 1) working along the line of prenatal treatment of Hemorrhagic Disease of the New Born, state that they believe that the blood of the foetus is in equilibrium with the maternal blood. Any deviation in the concentration of the clotting components would be manifested in the maternal blood studied early in the course of pregnancy. The evaluation of the blood clotting function of maternal blood would thus offer a basis of prediction of potential Hemorrhagic Disease of the New Born developing in utero. Such an early diagnosis would be more favorable for prenatal preventive therapy.

They report a case of a mother whose four previous babies died of Hemorrhagic Disease of the New Born. During the fifth pregnancy, the mother's blood was examined at the second month and found poor in clotting function and specifically low in prothrombin content - the characterizing deficiency factor in the blood of Hemorrhagic Disease of the New Born. The treatment of the mother consisted in an analysis of her nutritional habits, in order that her corrected food intake might be balanced and adequate, and particularly high in varied proteins (at least 6 gms. per kilogram of body weight) and varied lipins. The visceral organs were given because of their protein phospholipins

content, in this order: lung, kidney, testis, brain, heart, pancreas and liver. The acid-forming proteins were neutralized by base-forming fruits and vegetables. An excess of basic salts are requisite for a positive calcium balance as well as for their favorable effect on prenatal development. On this regimen, the mother's blood became normal, and a normal infant was delivered at full term.

The chemical nature of the clotting components has been established as lipins for the platelets, originating in the bone marrow; and globulins for the prothrombin and fibrinogen, synthesized in the liver. Thus lipins and globulins are the sources of the blood-clotting substances, initially arising from the daily dietary.

The nutritional regimen of the case cited (19) was as follows:

8:00 A. M. - A thromboplastic substance, fruits, fructose, cream, coarse cereal, butter, eggs and bacon, acidophilus milk.

12:00 A. M.- Calcium chloride in spleen marrow 15 cc. cooked and raw vegetables, raw visceral organs, bone marrow, stewed or raw fruits.

6:00 P. M.- Calcium chloride in spleen marrow, cooked vegetables, acidophilus milk, stewed and raw fruit.

Kugelmass and Samuel (18) as the result of their experimental work, conclude that the prolonged feeding of a diet containing protein, increases the coagulability of

the blood and maintains the clotting factors at a high level. This recent investigation is extremely interesting and prophylaxis will undoubtedly become more important.

CONCLUSION:

It has been shown that Hemorrhagic Disease of the New Born is a distinct disease entity, fairly frequent in occurrence and characterized by a prolonged coagulation and bleeding time, occurring in new born infants during the first week of life. It bears some relationship to the normal prolongation in coagulation time, occurring in new born infants, which reaches a maximum on the fifth day, and returns to the time of the first twenty-four hours before the tenth day of life.

The essential symptom is spontaneous bleeding, which may be from any mucus surface or into any organ or part of the body, evident or concealed, unassociated with any demonstrable anatomical pathology.

It has been demonstrated that there is a deficiency of prothrombin - an essential factor in the normal clotting process, in the infant's blood at this time. Various explanations have been offered, but the essential cause of this deficiency still remains undetermined.

The average new born infant during this time, is in a transitional period between release from the obstetrician and supervision by the pediatrician, with consequent diffusal of medical responsibility, and delay in early

recognition of symptoms and the institution of appropriate treatment. Early recognition and treatment are the important factors in prognosis.

Since blood studies permit of an earlier diagnosis than symptoms, coagulation and bleeding time determinations should be made routinely on every new born infant, on the first, third and fifth days of life. If the clotting time exceeds ten minutes or the bleeding time five minutes, even without symptoms, a prophylactic injection of 15 to 30 cc. of whole human blood should be given subcutaneously every six to eight hours until the coagulation and bleeding time return to normal and remain there.

These tests are simple and can be done by anyone; and only by early recognition can the disastrous results of intracranial hemorrhage be avoided. It has been shown that 50 percent of infants dying intrapartum or within a few days after birth, die from intracranial hemorrhage, and Hemorrhagic Disease of the New Born is the underlying basis of the majority of these fatalities.

If hemorrhage has already occurred, whole human blood should be administered intramuscularly, intraperitoneally or intravenously, depending on the severity of the condition and the experience of the operator. When blood is given intravenously, preliminary cross-agglutination tests are necessary, and the blood should be given in the amount of 10 to 15 cc. per pound of body weight. The treatment with human blood has lowered the mortality to only a fraction of

that occurring before this method of treatment was employed.

Recent investigation has shown that ~~am~~maternal diet high in the varied proteins and with a high water-soluble vitamine "B" content, is of value in the prenatal prevention of the disease. Ultra violet light also is valuable in prophylaxis.

What the future will bring is a matter of interesting conjecture, but the ultimate solution of the problem, may in all probability lie along the lines of the newer aspects of nutrition.

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UNIVERSITY HOSPITAL CASE NO. 15242.

BABY BROWN -- Born 11-27-24, male, wt. 9 lb. $\frac{3}{4}$ oz.

Labor was prolonged and difficulty was encountered in extraction of the after coming head. Six minutes elapsed before the head was delivered.

Resuscitation was difficult and infant did not cry but had shallow respiration with an occasional gasp. The buttocks were blue in color, the legs were in a semiflexed position and somewhat rigid. There was an occasional convulsive twitching of the left arm.

The infant was put to the breast and nursed well. There was an elevation of temperature to 104 in the afternoon, dropping to 102 in the evening.

On the second day the infant had a temperature of 101.

Careful observation was advised and spinal puncture if necessary. There was no bulging of the fontanelles but an intracranial hemorrhage was considered possible.

In the afternoon the infant became pale, refused to nurse and seemed very weak. The respiration was gasping and the cry weak. Caffeine Sodio-Benzate was given hypodermically. A spinal puncture was attempted but a dry tap obtained.

Infant died on the second day at 4:30 P. M.

Clinical Diagnosis -- Intracranial Hemorrhage.

NECROPSY.

An attempt was made to do a spinal puncture, but the needle went in too far in the lower lumbar region and pure blood was aspirated.

A cistern puncture was done and bloody spinal fluid with drawn.

Head -- The left side of the brain was found to be congested, as well as the choroid plexuses in the ventricles.

Abdomen -- There was a large quantity of free blood in the peritoneal cavity (this accounts for the free blood obtained on spinal puncture).

A large dark hematoma covered the right third of the liver, the hematoma being between the liver and its capsule. The capsule at this point was ruptured on the lower portion and blood was oozing from this site.

Pathological Diagnosis -- Hemorrhagic Disease of the New Born.

UNIVERSITY HOSPITAL CASE NO. 10594.

BABY GARCIA -- Born 3-27-23, female, wt. 8 lb. 1 oz.

The mother was a para 4, with a 4 plus Wasserman. Delivery was normal though somewhat prolonged.

The infant nursed well and was apparently normal until the third day when she nursed poorly and a shiny, red, raised area was found over the buttocks. This was considered to be of an inflammatory nature. The temperature was 103.5 and remained there until the seventh day when it dropped to 98.

On the fourth day the swelling began to extend up the back and around the umbilicus. The infant vomited a dark brown substance at intervals during the last few days.

On the seventh day there were tetanic contractions of the hands and feet, the tissues seemed firm and leathery. 10 cc of anti-streptococcus serum was given.

The coagulation time on the seventh day was 12 minutes and seven minutes on two determination.

Infant died on the seventh day.

NECROPSY.

Inspection - The body was that of a fairly well nourished infant. The hair was dark and fine. The skin was dark with erythematous patches over the back and lateral portion of abdomen, and of a leathery consistency. On palpation the tissues were non-elastic and extremely firm and rigid.

The buttock's showed a dark mottling. There was bleeding from the nose and mouth.

Abdomen - On cutting the abdominal wall, the tissues gave a firm resistance. The Peritoneum was glistening, and some clear fluid in the peritoneal cavity.

The liver, spleen and pancreas were normal.

The stomach was markedly distended with gas, showing multiple ulcerations about 1mm. in diameter over the entire wall, penetrating the mucosa and muscularis but not the serosa. On cut section a dark reddish substance resembling old clotted blood was noted in these ulcerative penetrations, which on scraping was found to be adherent.

The mucosa of the stomach was lined with fine granular clotted blood extending into the ulcerative penetrations.

The small intestine was negative, the appendix retrocecal and angulated.

The kidneys appeared to be of normal size and were lobulated. The capsule stripped easily and on cut section appeared normal.

Thorax - The normal clear fluid was present in the pleural cavity.

Both lungs showed multiple hemorrhagic areas resembling infarcts. The lateral posterior portions of the bases of both lungs were congested. The heart was normal, the foramen ovale functionally closed.

Special - On section the subcutaneous tissue of the buttocks was slightly greyish in color and showed subcutaneous hemorrhage. A smear was made of the expressed fluid and this showed pus cells, and on culture staphylococci were demonstrated.

Summary of Pathological Findings:

1. Purpura over buttocks.
2. Diffuse induration of the subcutaneous tissue .
3. Hemorrhage from nose and mouth.
4. Penetrating ulcerations of stomach wall with hemorrhage.
5. Hemorrhagic infarcts of lungs.
6. Subcutaneous staphylococcus infection over buttocks.

Primary cause of death.

Hemorrhagic Disease of New Born.

Contributory or immediate cause of death.

1. Gastric Hemorrhage.
2. Subcutaneous Infection.

UNIVERSITY HOSPITAL CASE NO. 12834.

BABY SMITH -- Born 1-26-24.

Labor was normal in every respect and a normal male baby delivered.

On the second day when the bowls moved, a large quantity of blood was passed. During the day several additional, severe hemorrhages occurred from the bowls. The case was diagnosed as Hemorrhagic Disease of the New Born and 14 cc of the mother's blood was injected into the buttocks.

On the third day the coagulation time was found to be seven minutes. The hemorrhage continued, the infant having 22 bowl movements in 24 hours. Mother's blood 18 cc was again injected into the buttocks.

During the evening of the third day there was muscular twitching of the left side of the face, the arms twitched and there was horizontal nystagmus to the left. The fontanelles were bulging so a spinal puncture was done, obtaining a bloody spinal fluid.

The infant had no further hemorrhage, there was no more bulging of the fontanelles and all signs of intracranial pressure disappeared.

On the seventh day there was some hemorrhage from

the umbilical cord which became more marked on the next day. It was necessary to apply a purse-string suture around the umbilicus to establish hemostasis.

A few days later the infant developed a yellow color of the skin, spasticity of the hands and finally died on the morning of the 16th day.

Laboratory Findings.

3rd day -- Coagulation Time -- 7 minutes.

12th day -- Coagulation Time -- 9 minutes.

Hemoglobin -- 30%

R. B. C. -- 3,200.00

W. B. C. -- 18,400

Polymorphonuclears -- 38%

Lymphocytes -- 62%

NECROPSY.

Inspection -- The body was that of a very young infant, very pale in color. The skin was shriveled and shrunken, suggesting loss of body fluid and dehydration. There were no petechiae, ecchymoses or bleeding from nose, mouth, eyes, umbilicus or anus.

The anterior fontanelle was open and there was no bulging.

Abdomen -- The peritoneum was smooth and there was no free fluid in the peritoneal cavity.

The liver was not enlarged but contained many dark brown pigmented areas. The intestine and stomach were very pale in color and did not show any hemorrhagic areas.

The spleen and pancreas were normal in size and appearance.

Thorax -- Both lungs were crepitant throughout.

The heart was firm and smooth. The pericardium was smooth.

Head -- There was a large quantity of blood which had distended the subarachnoid space on both sides. There was no flattening of the convolutions or hemorrhage into the brain substance.

Summary of Pathological Finds:

1. Extensive subarachnoid hemorrhage

Primary Cause of Death:

Hemorrhagic Disease of New Born

Contributory Cause of Death:

Subarachnoid Hemorrhage.

COMMENT:

In searching through the files of the University Hospital "Hemorrhagic Disease of the New Born" was not listed in the index. However, the death records were gone over and three cases were discovered. No effort was made to secure cases outside the University Hospital, since it was felt that laboratory work would probably be lacking or inadequate, and that they would possess no advantage over cases reported in the literature.

University Hospital Case No. 15242: Labor was difficult and prolonged. The infant showed immediate evidence of intracranial hemorrhage, as indicated by the muscular twitching and rigidity; due undoubtedly to the trauma of delivery. On the afternoon of the second day, evidences of severe internal hemorrhage appeared. At autopsy, intracranial hemorrhage and a rupture of the capsule of the liver were demonstrated. No bleeding or coagulation time determinations were made. In the absence of these tests, the findings are inconclusive.

University Hospital Case No. 10594: The symptoms given, as occurring on the third day, were rather vague, but probably indicated hemorrhage. However, there was also evidence of infection. On the seventh day there were manifest signs of hemorrhage, with evidences of a

severe infection which on autopsy was found to be B. staphylococcus. The coagulation time on the seventh day was found to be seven and twelve minutes on two determinations, giving an average for the two tests of nine and one-half minutes. This is not above the accepted normal range. In the absence of a prolongation of coagulation time, and with no bleeding time determinations having been made, this may have been a symptomatic hemorrhage as a result of infection, rather than a manifestation of true Hemorrhagic Disease of the New Born.

University Hospital Case No. 12834: This infant showed all the manifestations of Hemorrhagic Disease of the New Born, both in symptoms and course. However, the coagulation time on the third day was seven minutes, and according to accepted standards this falls within the normal range, but no bleeding time determinations were made. The Hemorrhagic Disease of the New Born is a complex of delayed coagulation and increased bleeding time.

The history given in the case records is inadequate, and the evidence is confusing. The reasons for the failure to include these cases in the Thesis, are quite obvious.